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Huber, Carola A ; Rapold, Roland ; Brüngger, Beat ; Reich, Oliver ; Rosemann, Thomas

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One-year adherence to oral antihyperglycemic medication and risk prediction of patient outcomes for adults with diabetes mellitus

An observational study

Carola A. Huber (PhD, MPH)^{a,*}, Roland Rapold (PhD)^a, Beat Brüngger^a, Oliver Reich (PhD)^a, Thomas Rosemann (MD, PhD)^b

Abstract

Medication adherence is essential in preventing adverse intermediate outcomes, but little is known on hard outcomes. The aims of this study were to determine the 1-year adherence to oral antihyperglycemic drugs (OADs) and to predict the risk of subsequent health outcomes among (non)adherent patients with diabetes.

Using a large Swiss healthcare claims database from 2011 to 2014, we identified all patients aged ≥ 18 years with diabetes and treated with at least 1 OAD prescription. Adherence to OADs was measured as the proportion of days covered (PDC) over 1 year and subdivided into 2 categories: adherent (PDC $\geq 80\%$), nonadherent (PDC $< 80\%$). We estimated the relative risk of hospitalization and mortality at follow-up using multivariate Cox proportional hazard models.

Based on a sample of 26,713 patients, adherence to OADs was quite low: 42% of the patients achieved a PDC of $\geq 80\%$ during the 1-year observation period. A 7% reduction in the hospitalization risk and a 10% reduction in the risk of mortality could be observed in adherent patients compared to nonadherent patients (hazard ratio [HR], 0.93 [95% CI, 0.89–0.97]; HR, 0.90 [95% CI, 0.82–0.99]). Subgroup analysis showed that an intensified diabetes therapy had no significant influence on the risk of both outcomes in adherent patients.

Poor medication adherence increases the risk of subsequent hospitalizations and premature mortality in patient with diabetes, regardless of disease severity and comorbidities. This emphasizes the need for an earlier identification of patients with poor medication adherence. The awareness of physicians and patients regarding the importance of adherence in diabetes treatment should be increased.

Abbreviations: ATC = Anatomical Therapeutic Chemical, HbA1c = hemoglobin A1c, HR = hazard ratio, MPR = medication possession rate, OAD = oral antihyperglycemic drug, PDC = proportion of days covered, WHO = World Health Organization.

Keywords: diabetes, hospitalization, medication adherence, mortality, oral antihyperglycemic drugs

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1. Introduction

Medication adherence is considered as a key issue in the quality of diabetes care. An appropriate pharmacotherapy is essential for an effective diabetes management and in the meanwhile also driven by a high awareness of physicians and other care providers.^[1] The benefits of diabetes treatment adherence to intermediate outcomes in patients with diabetes were investigated in several empirical studies.^[2] For example, previous research on antihyperglycemic adherence primarily examined the association between adherence and glycemic control, showing a significantly improved value of hemoglobin A1c (HbA1c) among patients with high adherence.^[3,4] In contrast, data on the impact of medication adherence on further subsequent health outcomes are relatively scarce. Some studies showed a reduced risk of hospitalization, when patients continuously obtain oral antihyperglycemic drugs (OADs).^[5–7] There is also limited evidence showing a beneficial effect of diabetes medication adherence on mortality, for example, in a US managed care setting, and on healthcare costs, for example, among newly diagnosed Korean patients.^[8,9] Furthermore, existing findings on medication adherence were based on outdated data, rather small sample

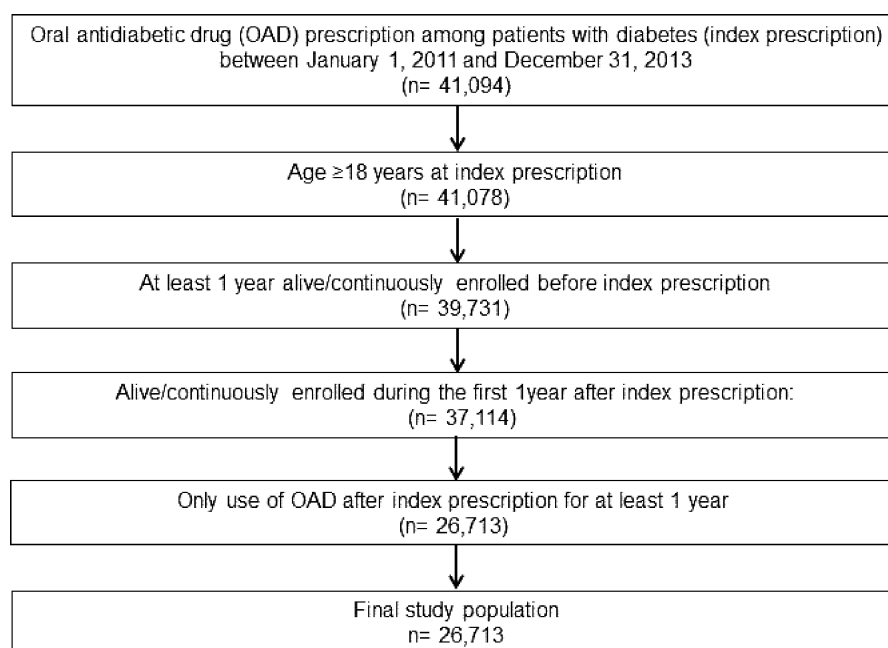


Figure 1. This flowchart provides an overview of the included patients.

sizes, and on data from Asian and US populations. Thus, it is unclear whether the association is also given in a European context. In addition, there is no standardized measurement of adherence in a context of a wide range of adherence measures.^[10] One of the most commonly used method is the so-called medication possession rate (MPR).^[5,9,11,12] The MPR is a method, which quantifies medication adherence by summing up the days' supply for all prescribed drugs and afterwards by dividing the number of days within the given observation period. Since the MPR does not adjust for concurrently used drugs within a medication class, the MPR tends to overestimate adherence. To overcome this potential bias, recently published literature recommend to calculate the proportion of days covered (PDC) as a preferred method of measuring medication adherence, which is a more conservative and precise instrument than the MPR.^[13,14] In this study, we aimed to apply the PDC, 1st to determine the medication adherence in a large cohort of diabetes patients receiving treatment with OADs, and 2nd to predict the relative risk of hospitalization and mortality in adherent patients compared to those who were not adherent.

2. Methods

2.1. Study design and population

We performed a retrospective cohort study using a large health insurance claims database from January 1, 2011 to December 31, 2014. Claims data were derived from the leading health and accident insurance company in Switzerland (Helsana Group), which covers over 1 million Swiss mandatory insured persons. The database comprises information on populations' sociodemographics, type of health insurance, outpatient and inpatient health care utilization, laboratory, and drug data. Drug data are coded according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) Classification System and are based on all medications which were prescribed in the

outpatient setting and purchased directly by the dispensing physician or at the pharmacy.^[15] Since the recorded claims cover almost all health care invoices, these data are highly reliable. The study population included continuously enrolled adult patients who were diagnosed with a "glucose metabolism disorder (diabetes mellitus)" or had at least 1 prescription of an antihyperglycemic medication in the year before index date. The index date was the 1st prescription of an oral antihyperglycemic medication during the recruiting period, which extends to the 1st 3 years of the total study period (through December 31, 2013). After index date, patients had to be alive and continuously enrolled for at least 1 year in order to obtain an appropriate observation period for patients' medication adherence. We also excluded patients receiving any insulin prescription through the period after index date. Eligible patients were afterwards followed until the occurrence of the outcome, disenrollment, death, or the end of the study (December 31, 2014). Figure 1 shows how patients with diabetes were selected for the cohort study (flowchart). According to the national ethical and legal regulation, an ethical approval was not needed.

2.2. Medication adherence

Medication adherence to oral antihyperglycemic medication was measured by PDC.^[13,14] We calculated the PDC for each patient as the number of days of medications supplied between the 1st prescription (x, index date) and the last date (y) of a 1-year interval following the index date, divided by the total days of the interval. The equation for the PDC is as follows:

$$\text{PDC} = \frac{\text{days supplied between x and y}}{365 \text{ days}} \times 100\%$$

We defined the number of days supplied based on the defined daily doses for each OAD class. The defined daily dose reflects the average daily dose for a drug used for its main indication in adults

recommended by the WHO.^[15] If days of supply added up to more than 365 days, the supply was truncated at 365 days, reflecting a maximum PDC of 100%. The PDC was based on prescriptions for the following OAD classes according to the WHO ATC Classification System: biguanides (A10BA), sulfonamides (urea derivatives, A10BB), sulfonamides (heterocyclic, A10BC), combinations of oral blood glucose lowering drugs (A10BD), alpha glucosidase inhibitors (A10BF), thiazolidinediones (A10BG), dipeptidyl peptidase 4 inhibitors (A10BH), other blood glucose lowering drugs, and excl. insulins (A10BX). Patients receiving glucagon-like peptide-1 receptor agonists were excluded. Since the different drug classes belong to 1 therapeutic group and some patients with diabetes are recommended to take 2 or more OADs concurrently, we considered all classes interchangeable. Patients were classified as adherent if their individual PDC was $\geq 80\%$, respectively, as nonadherent with a PDC of $<80\%$, which is a recommended cut-off point in literature.^[16]

2.2.1. Outcomes and covariates. The outcome measures included all-cause hospitalization and all-cause mortality during the follow-up period (January 1, 2012 to December 31, 2014). All-cause hospitalization was defined as at least 1 overnight stay in an acute-care hospital during patients' follow-up period. Several patient characteristics were included as covariates in the regression models comprising age, sex, and health insurance plan (managed care enrollment, high deductible class of >500 vs ≤ 500 Swiss Francs), all measured at index date. Furthermore, we added following 3 indicator variables for patients' health status: preceding hospitalization, number of comorbidities, and diabetes drug therapy. Preceding hospitalization was defined as an overnight stay in an acute-care hospital in the year before index date. Since national disease registers recording clinical diagnoses are not available, we used prescription data to identify patients' comorbidities in the year before index date. This approach is a commonly used and well validated morbidity measure, which indicates the occurrence of a broad range of (chronic) diseases.^[17,18] Additionally, we created a categorical variable to indicate the intensity of diabetes drug therapy over 1 year after index date by distinguishing between 3 different treatment intensifications: metformin-only therapy, therapy with metformin and another OAD, and therapy with other combinations of OADs. The measurement of all 3 forms of diabetes therapy relates to the summary of all prescribed OAD classes (according to the WHO ATC Classification System) that we have recorded in our database during the 1-year observation period of adherence (1 year after index date).

2.3. Statistical analysis

We performed Chi-square tests and Kruskal–Wallis tests to compare baseline characteristics between nonadherent patients (PDC $<80\%$) and adherent patients (PDC $\geq 80\%$). In order to display the distribution of the PDC, a density plot was provided for the PDC (as continuous variable) for the nonadherent and the adherent patient group. Multivariate Cox proportional hazards regression models were used to estimate the relative risk of medication adherence on hospitalization and mortality, controlling for age, sex, health insurance plan, preceding hospitalization, number of comorbidities, and diabetes therapy. Hazard ratios (HRs) together with the 95% confidence intervals (95% CIs) are presented. We performed the Cox regression models using the PDC both as binary variable (PDC $<80\%$ /PDC $\geq 80\%$) and as continuous variable. All analyses were conducted using R version

3.2.0 (R Development Core Team 2015). A P -value <0.05 was considered as statistically significant.

3. Results

A total of 26,713 patients using OADs met the criteria for inclusion. Table 1 reports the baseline characteristics for the total study population as well as for the subdivided sample by adherence status. Most of the total study population were men, had a standard insurance health plan and a mean age of 69 years. The most common therapy was metformin-only (41%). About a 3rd was treated with metformin and another OAD (32%) and more than a quarter received a therapy with other combinations of OADs (27%). Almost 75% of the patients with diabetes suffered from more than 1 comorbidity and nearly 10% had been hospitalized 1 or more times during the year before index date. The proportion of patients who were adherent to OAD therapy was poor. Only 42% of the patients achieved a PDC of at least 80% during the 1 year observation period. The mean PDC was 68% in the total, 49% in the nonadherent and 94% in the adherent patient group. As shown in the density plot of patients' PDC (Figure 2), the distribution of the PDC was continuously low among the nonadherent patients, whereas the adherent patients had a high proportion of those with a PDC $>90\%$. When classified by the adherence status, significant differences could be observed in almost all patient characteristics between adherent and non-adherent patients. Compared with adherent patients, nonadherent patients had statistically significant more frequent a preceding hospitalization, a slightly higher proportion of patients with at least 5 comorbidities, and received mostly metformin-only therapy ($P \leq 0.001$). Half of the group of adherent patients had a more intensified treatment with metformin and another OAD (50%).

Table 2 presents the adjusted risk for all-cause hospitalization. We estimated a 7% reduction in the risk of hospitalization among adherent patients compared to nonadherent patients (HR, 0.93 [95% CI, 0.89–0.97]), after adjustment for confounding. Furthermore, the risk of hospitalization increased with age, the number of comorbidities and the intensity of diabetes therapy. Among nonadherent patients, receiving a diabetes therapy with metformin and another OAD was associated with the highest risk of hospitalization compared to other therapies (HR, 1.09 [95% CI, 1.02–1.17]). In addition, the hospitalization risk increased strongly when patients suffering from more than 4 comorbidities (HR, 1.87 [95% CI, 1.72–2.02]). Adherent patients also had an increased risk for hospitalization with an increased number of comorbidities, but there was no significant influence of the kind of diabetes therapy.

As shown in Table 3, adherent patients had a 10% reduction in the risk of mortality compared with nonadherent patients, after adjustment for confounding (HR, 0.90 [95% CI, 0.82–0.99]). Risk of mortality increased significantly with age, intensity of therapy, and number of comorbidities. Nonadherent patients had an almost twice as high risk for death, when they were suffering from multimorbidity with more than 4 concurrent conditions (HR, 1.96 [95% CI, 1.66–2.32]). This association is slightly weaker with an HR of 1.83 (95% CI, 1.50–2.24) in the adherent patient group. Whereas the therapy intensity had no significant influence on the mortality risk in adherent patients, the 2 combined OAD therapies increased the risk for almost a quarter with an HR of 1.23 (95% CI, 1.06–1.41) and 1.24 (95% CI, 1.10–1.40) in the nonadherent patients. Additional analyses, in which we used the PDC as continuous variable, confirmed the positive effect of medication adherence on patients' hospitaliza-

Table 1
Patient characteristics at baseline by medication adherence.

Variable	Total		Nonadherent patients (PDC ≤ 80)		Adherent patients (PDC ≥ 80)		P
	n	%	n	%	n	%	
Population	26,713	100.0	15,399	57.6	11,314	42.4	
Gender							≤0.01
Male	14,337	53.7	7985	51.9	6352	56.1	
Female	12,376	46.3	7414	48.1	4962	43.9	
Mean age (years [SD])	69.0 (11.9)		68.8 (12.4)		69.4 (11.0)		0.07
Age in groups							≤0.01
18–44	751	2.8	562	3.6	189	1.7	
45–54	2421	9.1	1470	9.5	951	8.4	
55–64	5633	21.1	3216	20.9	2417	21.4	
65–74	8381	31.4	4602	29.9	3779	33.4	
75–84	7396	27.7	4216	27.4	3180	28.1	
≥85	2131	8.0	1333	8.7	798	7.1	
Insurance plan							
Managed care	8011	30.0	4652	30.2	3359	29.7	0.37
High deductible class (>500 Swiss Francs)	1439	5.4	961	6.2	478	4.2	≤0.01
Preceding hospitalization	2549	9.2	1677	10.9	872	7.7	≤0.01
Diabetes therapy							≤0.01
Metformin only	11,035	41.3	9181	59.6	1854	16.4	
Metformin + another OAD	8551	32.0	2875	18.7	5676	50.2	
Other combinations of OADs	7126	26.7	3343	21.7	3784	33.4	
PDC							≤0.01
Mean PDC (SD)	67.9 (26.9)		49.0 (19.7)		93.5 (6.4)		
Median PDC (IQR)	72.8 (44.5)		50.3 (31.9)		95.1 (11.8)		
Number of comorbidities							≤0.01
0–1	6817	25.5	4097	26.6	2720	24.0	
2–4	15,041	56.3	8438	54.8	6603	58.4	
≥5	4855	18.2	2864	18.6	1991	17.6	

IQR=inter-quartile range, OAD=oral antihyperglycemic drug, PDC=proportion of days covered, SD=standard deviation.

tion and mortality risk among the total and the nonadherent patient group (Table S1, Table S2, <http://links.lww.com/MD/B61>). We could not observe a significant effect on both outcomes in the adherent group.

4. Discussion

The main finding of this study was that adherence to antihyperglycemic medication is significantly associated with a

7% decrease in risk of hospitalization and a 10% reduction in mortality risk compared with nonadherence in patients with diabetes. This finding is in line with the limited previous research showing improved intermediate outcomes due to better adherence to drug therapy in patients with diabetes. For example, a systematic review revealed that high adherence was associated with improved glycemic control in patients with diabetes.^[2] But as this review summarized, previous work mainly focused on the

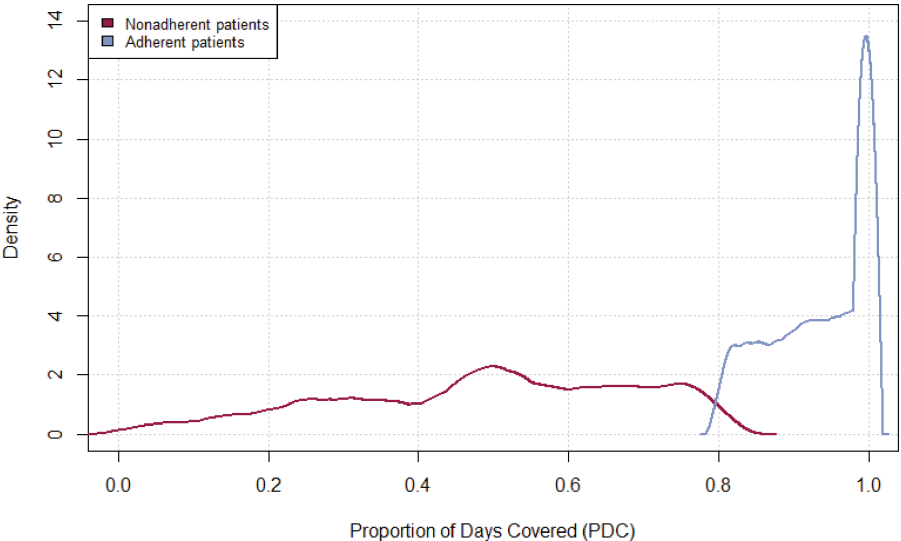


Figure 2. This figure displays two density plots.

Table 2**Cox proportional hazard analysis of all-cause hospitalization and PDC (<80%/≥80%).**

Variable	Hospitalization risk					
	Total		Nonadherent patients (PDC < 80%)		Adherent patients (PDC ≥ 80%)	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Gender						
Male	1.00		1.00		1.00	
Female	0.88 (0.84–0.91)	≤0.001	0.92 (0.88–0.97)	≤0.01	0.82 (0.77–0.87)	≤0.01
Age in groups						
18–44	1.00		1.00		1.00	
45–54	0.997 (0.84–1.19)	0.975	1.01 (0.82–1.24)	0.016	1.02 (0.73–1.42)	0.923
55–64	1.30 (1.10–1.53)	≤0.01	1.27 (1.05–1.54)	≤0.001	1.38 (1.01–1.90)	≤0.05
65–74	1.75 (1.49–2.06)	≤0.001	1.69 (1.40–2.04)	≤0.001	1.90 (1.40–2.60)	≤0.01
75–84	2.32 (1.98–2.73)	≤0.001	2.30 (1.91–2.77)	≤0.001	2.45 (1.80–3.34)	≤0.01
≥85	2.65 (2.24–3.13)	≤0.001	2.51 (2.06–3.06)	≤0.001	2.98 (2.16–4.10)	≤0.01
Insurance plan						
Managed care	0.96 (0.92–1.002)	0.059	0.95 (0.90–1.01)	0.081	0.97 (0.91–1.03)	0.334
High deductible class (>500 Swiss Francs)	0.79 (0.71–0.87)	≤0.001	0.79 (0.69–0.89)	≤0.001	0.80 (0.68–0.95)	≤0.01
Preceding hospitalization	1.49 (1.41–1.58)	≤0.001	1.51 (1.41–1.63)	≤0.001	1.45 (1.32–1.60)	≤0.01
High adherence (PDC ≥ 80)	0.93 (0.89–0.97)	≤0.001				
Diabetes therapy						
Metformin only	1.00		1.00		1.00	
Metformin and another OAD	1.05 (1.003–1.11)	≤0.05	1.09 (1.02–1.17)	≤0.01	1.03 (0.95–1.12)	0.516
Other combination of OADs	1.07 (1.02–1.12)	≤0.01	1.05 (0.98–1.11)	0.142	1.08 (0.99–1.18)	0.10
Number of comorbidities						
0–1	1.00		1.00		1.00	
2–4	1.28 (1.21–1.34)	≤0.001	1.29 (1.21–1.38)	≤0.001	1.25 (1.16–1.36)	≤0.01
≥5	1.83 (1.73–1.95)	≤0.001	1.87 (1.73–2.02)	≤0.001	1.78 (1.62–1.95)	≤0.01

95% CI = 95% confidence interval, OAD = oral antihyperglycemic drug, PDC = proportion of days covered.

Table 3**Cox proportional hazard analysis of all-cause mortality and PDC (<80%/≥80%).**

Variable	Mortality risk					
	Total		Nonadherent patients (PDC < 80%)		Adherent patients (PDC ≥ 80%)	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Gender						
Male	1.00		1.00		1.00	
Female	0.69 (0.63–0.74)	≤0.001	0.76 (0.68–0.85)	≤0.001	0.59 (0.52–0.68)	≤0.01
Age in groups						
18–44	1.00		1.00		1.00	
45–54	3.61 (0.86–15.17)	0.080	5.60 (0.75–42.10)	0.094	1.82 (0.23–14.25)	0.567
55–64	7.73 (1.91–31.24)	≤0.01	9.72 (1.35–70.06)	≤0.05	5.06 (0.70–36.43)	0.108
65–74	16.23 (4.04–65.13)	≤0.001	21.92 (3.07–156.41)	≤0.01	9.85 (1.38–70.31)	≤0.05
75–84	49.06 (12.25–196.55)	≤0.001	72.17 (10.14–513.55)	≤0.001	27.09 (3.81–192.84)	≤0.01
≥85	142.28 (35.50–570.31)	≤0.001	201.09 (28.24–1431.68)	≤0.001	83.09 (11.65–592.37)	≤0.01
Insurance plan						
Managed care	0.86 (0.77–0.94)	≤0.01	0.85 (0.75–0.97)	≤0.05	0.86 (0.74–0.99)	≤0.05
High deductible class (>500 Swiss Francs)	0.86 (0.68–1.07)	0.169	0.83 (0.63–1.10)	0.194	0.92 (0.64–1.33)	0.671
Preceding hospitalization	1.45 (1.29–1.63)	≤0.001	1.42 (1.23–1.65)	≤0.001	1.50 (1.24–1.82)	≤0.01
High adherence (PDC ≥ 80)	0.90 (0.82–0.99)	≤0.05				
Diabetes therapy						
Metformin only	1.00		1.00		1.00	
Metformin and another OAD	1.18 (1.06–1.31)	≤0.01	1.23 (1.06–1.41)	≤0.01	1.05 (0.87–1.27)	0.601
Other combination of OAD	1.18 (1.07–1.31)	≤0.01	1.24 (1.10–1.40)	≤0.001	1.04 (0.85–1.26)	0.736
Number of comorbidities						
0–1	1.00		1.00			
2–4	1.24 (1.10–1.39)	≤0.001	1.25 (1.07–1.45)	≤0.01	1.22 (1.02–1.46)	≤0.05
≥5	1.92 (1.69–2.18)	≤0.001	1.96 (1.66–2.32)	≤0.001	1.83 (1.50–2.24)	≤0.01

95% CI = 95% confidence interval, OAD = oral antihyperglycemic drug, PDC = proportion of days covered.

association between adherence and intermediate outcomes. However, there is some evidence for the beneficial effect of medication adherence on further important patient outcomes. For example, Sokol et al.^[6] could show that high levels of medication adherence (measured as adherence rates) were associated with lower disease-related medical costs and hospitalization rates. Some further studies also revealed that non-adherence to antihyperglycemic medication (measured as MPR) leads to an increased risk of hospitalization, health care costs, and mortality.^[5,9] However, it is difficult to compare our findings with those from existing work, which was based on varying measures of adherence, rather outdated data, or on subpopulations including only newly treated patients. Therefore, the present study expands the existing literature on medication adherence in patients with diabetes and highlights the importance of the adherence to oral hyperglycemic medication regarding avoidable adverse patient outcomes such as hospitalization and premature mortality.

The analysis of subgroups revealed 3 further important findings: first of all, when we used the PDC as continuous variable and performed subgroup analysis for the nonadherent and the adherent patient group, we could also observe that the effect of the PDC is meaningful on the patient outcomes. The lower the PDC the higher the risk among nonadherent patients. In contrast, among patients who were already in the adherent group, an increase of the PDC did not further influence the hospitalization and mortality risk. Second, we could prove that the benefit of adherence remains with the increase of the complexity of the diabetes therapy, since the group with additional diabetes drugs (most likely reflecting disease severity) showed a lower risk of hospitalization as well as a reduced risk of mortality. In this context, the Action to Control Cardiovascular Risk in Diabetes trial has been discussed often if intensified diabetes treatment may have harmful effects due to side effects of the drugs or increased number of hypoglycemic events.^[19] However, even we have no HbA1c levels and cannot conclude on the glycemic control, we can state that we could not observe any evidence showing negative effects of the escalation of the medication. The third important subgroup finding was, that even with additional diseases, patients take advantage of adherence, since these patients also showed a significantly reduced risk of hospitalization and mortality compared to nonadherent patients. Multimorbidity is often regarded as a reason for negative drug effects and as reasoning for depression, especially among elderly patients.^[20] Our results contribute to this discussion at least in a way that adherence is beneficial even in multimorbidity.

Besides the main finding of our study, the study also revealed that the medication adherence in patients with diabetes was quite low. Only 42% of the patients were adherent ($\geq 80\%$ PDC) to OAD therapy during the 1 year observation period. This result is in line with the lowest value from findings of 2 systematic reviews on adherence to diabetes medication, which reported an adherence rate ranging from approximately 40% to 90%.^[21,22] Furthermore, we could observe that the PDC was continuously quite low in the nonadherent patient group, but the proportion of the adherent patients with a PDC with $>90\%$ was high. Whereas we found the highest proportion of nonadherent patients in patients using metformin only, most adherent patients were treated with combinations of OADs (metformin and another OAD, other combinations of OADs). This is conflicting with previous work, which showed a higher proportion of adherent patients than in nonadherent patients in users of oral

hypoglycemic only.^[8] However, comparing results is challenging due to the small amount of evidence available, which investigated this association. Moreover, it is difficult to compare adherence rates with each other, since the study design, the included populations, the used medications classes, and especially the applied measurement of adherence can completely differ between the studies. According to the current literature, the PDC is the recommended instrument to measure medication adherence, which provides rather conservative estimates and accounts for clinical situations when patients switch drugs or use multiple medications concurrently.^[10,13] Thus, we stress the need for the introduction of a standardized measure of medication adherence such as the PDC in future studies on diabetes care.

Some strengths and limitations of our study have to be acknowledged. The major strength of our study is that it is, to the best of our knowledge, the first study investigating the impact of adherence to diabetes medication on hospitalization and mortality in Europe. Another strength is that the findings were based on a comprehensive dataset including a large amount of patients treated in primary care. Furthermore, we included a real-life patient sample, comprising both elderly and nonelderly patients, and did not exclude subpopulations as it is used most often in randomized control trials (e.g., patients aged over 65 years and older, or those without comorbidity). Additionally, we applied the most recent and recommended adherence measurement, which allows a more realistic estimate of medication adherence than previously used measurements, and thus avoiding overestimation. Our study has also limitations. First of all, there might be a bias regarding identification of patients with diabetes, since we could not include patients who receive only lifestyle treatment. Furthermore, we measured adherence by the PDC, which might be a good measure, but in the end does not reflect real intake of the drugs. A further weakness is that we did not have any clinical parameters as diabetes duration, but also no laboratory data as, for example, the HbA1c level. So, we could not conclude from adherence to glycemic control.

In conclusion, poor medication adherence increases the risk of subsequent hospitalizations and premature mortality in patient with diabetes, regardless of disease severity and comorbidities. This has a high clinical impact and emphasizes the need for an earlier identification of patients with poor medication adherence. The awareness of physicians as well as patients regarding the importance of adherence in diabetes treatment should be increased.

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